REMARKS

Applicants have carefully studied the Office Action mailed on August 7, 2003, which issued in connection with the above-identified application. The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 1-35 are pending and at issue in the application. Claims 24-35 have been withdrawn from consideration as drawn to a non-elected invention. Claims 1-23 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1, 5, 7, 9, 10-12, 15, 17, and 19-23 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Claims 19 and 21-23 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Knapp *et al.* (FASEB J., 1995, 9:516-25). Claim 20 has been rejected under 35 U.S.C. §103(a) as being obvious over Knapp *et al.* in view of Cvejic *et al.* (J. Biol. Chem., 1997, 272:26959-64) and further in view of Egan *et al.* (Science, 1981, 214:923-4).

Claims 1-19 have been amended to more particularly point out and distinctly claim the invention. Specifically, claims 2-10 and 12-18 have been amended to add the terms "subunit" and "protein" to clarify the distinction between the terms "receptor" and "receptor subunit". Support for the terms "receptor subunit" and "protein" can be found, for example, at page 5, line 19 - page 6, line 2 and page 10 line 27 - page 11 line 8 of the specification. Following the Examiner's suggestion, claims 1, 11 and 19 have been amended to delete the term "expressed

endogenously"; claim 11 has been further amended to recite "wherein the host cell does not endogenously express the receptor subunits", and claim 19 has been amended to recite "wherein both receptor subunits are heterologously expressed in a host cell". Support for these newly introduced recitations can be found, for example, at page 19, lines 26-29, page 28, line 28 - page 29, line 2, and Examples 1-4 (in particular, page 61, lines 19-23). Claims 1, 11, and 19 have been also amended to correct formal defects by replacing the phrase "which receptor comprises" with "wherein said receptor comprises," as per the Examiner's suggestion. No new subject matter has been added as a result of the amendments, no new search is required, and no new issues are raised.

Restriction Requirement

Applicants respectfully acknowledge that the Examiner withdrew his request for election of a specific kind of receptor heterodimer presented in the Restriction Requirement of April 25, 2003, and rejoined Groups I-X (claims 1-23) to be examined together in the present application.

Claim Objections

In response to the Examiner's objections to claims 1, 11 and 19 and their dependent claims 2-10, 12, 13-18, and 20-23, the phrase "which receptor comprises" in claims 1, 11 and 19 has been replaced with the phrase "wherein said receptor comprises".

35 U.S.C. § 112, Second Paragraph Rejections

In the Action, claims 1-23 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner states at page 3, lines 1-2 of the Office Action that "claims 1-23 are confusing since it is not clear whether the claimed dimers are a fusion protein or cross-linked."

Applicants respectfully disagree with the Examiner's statement and note that the present invention takes advantage of the property of opioid and other G-protein coupled receptors (GPCRs) to form heterodimers of separate protein subunits, and the term "heterodimeric receptor" in the claims refers to this characteristic. Thus, heterodimeric receptor subunits recited in the present claims neither have to be fused to each other as parts of a fusion protein, nor have to be chemically cross-linked. As specified, *e.g.*, at page 5, line 19 - page 6, line 2 of the specification, the heterodimeric receptors of the invention comprise two separate protein subunits, an opioid receptor subunit and a second GPCR subunit. These receptor subunits may be expressed from two different expression vectors introduced in the same host cell. Applicants further note that, as specified, *e.g.*, at page 5, lines 24-26; page 41, lines 12-22; Example 4 (pp. 63-64) and the original claims 9 and 10, one or both of the receptor subunits may be represented by a fusion protein comprising, *e.g.*, an epitope tag (*e.g.*, FLAG or myc) for antibody recognition or a fluorescent tag (*e.g.*, luciferase or yellow fluorescent protein (YFP)) for Bioluminescence Resonance Energy Transfer (BRET) analysis. This does not mean, however, that these receptor subunits have to be fusion proteins or have to be expressed as a single protein, where the two subunits are fused to each other. Similarly, it is disclosed, *e.g.*, in Example 1 (see page 51, lines 9-15, page 53, lines 11-13) and Figure 1A, that the two receptor subunits may be cross-linked to increase the stability of a dimer. However, cross-linking is not necessary and, for some

heterodimers, does not affect the stability. Accordingly, the subunits of the heterodimeric receptors recited in the present claims do not have to be cross-linked.

In the Action, the Examiner also contends that the distinction between the terms "receptor" and "receptor subunit" in the claims is unclear. Applicants respectfully note that, as disclosed at page 10, line 27 - page 11, line 8 of the present application, the term "receptor subunit" refers to a single GPCR protein that associates with another GPCR protein to form a dimer. In contrast, the term "receptor" refers to the whole GPCR dimer. To clarify the distinction between the terms "receptor" and "receptor subunit", applicants have amended claims 2-10 and 12-18 to add the terms "subunit" and "protein".

The Examiner further states that "claims 1-10 are confusing since it is not clear how the heterodimer can be 'isolated' when both receptor subunits are expressed endogenously in the same cell." In response, applicants respectfully note that the definition of the term "isolated" provided at page 13, line 17 - page 14, line 8 of the present specification encompasses material "present in a cell extract" and material "present in a heterologous cell or cell extract" (emphasis added; see, in particular, page 13, lines 21-22). This term further encompasses proteins which may be associated with other proteins and with cellular membranes (see page 14, lines 4-6). To clarify this further, claim 1 has been amended to delete the term "endogenously".

The Examiner contends that is not clear how claims 11-18 would be distinct from the prior art, if forming heterodimers were an inherent property of opioid receptors. He also states that claims 19-23 are confusing since it is not clear whether the method is being performed on a heterologously expressed heterodimer as opposed to the endogenous opioid receptor in a cell.

Applicants respectfully submit that, as specified at page 19, lines 26-29 of the present specification, "[i]n the context of the present invention, the opioid receptor gene and a second receptor gene are heterologous to the vector or vectors in which they are inserted for cloning or expression, and they are heterologous to a host cell containing such a vector, in which it is expressed..." (emphasis added). As further specified at page 28, line 28 - page 29, line 2 and in Examples 1-4, to obtain heterodimers, opioid receptor subunits were heterologously co-expressed in cells which do not endogenously express these proteins, *e.g.*, in CHO, HEK 293 and COS cells, which "lack opiate binding" (see, *e.g.*, page 61, lines 19-23). Accordingly, as suggested by the Examiner, applicants have (i) amended claim 11 to recite "wherein the host cell does not endogenously express the receptor subunits" and (ii) amended claim 19 to substitute the recitation "wherein both receptor subunits are expressed endogenously in the same type of cell" with the recitation "wherein both receptor subunits are heterologously expressed in a host cell".

In light of the above-presented amendments and arguments, the rejections under 35 USC §112, second paragraph, are believed to be overcome and withdrawal of such is kindly requested.

35 U.S.C. §112, First Paragraph Rejections

In the Office Action, claims 1, 5, 7, 9, 10-12, 15, 17, and 19-23 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for opioid-chemokine heterodimers or any heterodimers other than opioid-opioid, opioid-dopamine and opioid-adrenergic receptor. The Examiner contends that it is not predictable which receptors form dimers with opioid receptors, while the specification provides no guidance or working examples for heterodimers other than opioid-opioid, opioid-dopamine and opioid-adrenergic receptor.

Applicants respectfully disagree with the Examiner and note that the present specification provides a very detailed disclosure of methods for obtaining various opioid-GPCR heterodimeric receptors by co-expressing them in heterologous host cells. The specification also discloses methods for identifying, isolating and studying these heterodimeric receptors using, *e.g.*, immunoprecipitation, receptor modulators, and BRET analysis. Finally, the specification discloses several specific opioid-GPCR heterodimeric receptors. On the basis of this disclosure, one skilled in the art would be easily able to create additional opioid-GPCR heterodimeric receptors encompassed by the present claims. Such identification would require only routine experimentation.

With respect to enablement for opioid-chemokine heterodimers, applicants respectfully submit that, contrary to the Examiner's assertion, at page 33, line 27 - page 34, line 9, the instant specification discloses that (i) given the approaches disclosed in the present invention, anyone skilled in the art would be in the position to experimentally demonstrate the existence of, *e.g.*, kappa-CCR5 and kappa-CXCR4 heterodimers, and (ii) the existence of such heterodimers is consistent with the observed feedback of opiates on immune system function. Indeed, using immunoprecipitation methods disclosed in the present application, Suzuki *et al.* (Exp Cell Res., 2002, 280:192-200; abstract attached as Exhibit A) have recently demonstrated that CCR5 chemokine receptor forms heterodimers with mu, delta, and kappa opioid receptors.

It is believed that the Examiner imposes an overly high and burdensome duty on applicants, one not required by Section 112 or by the case law[4]. Thus, according to the current law and patent practice, the specification can permit some inferences to be drawn by those skilled in the art, and still comply with the enablement and written description requirement. In

[4] *See*, in particular, *In re Wands*, 858 F.2d 731-40, 8 USPQ2d at 1400-07 (Fed. Cir. 1988).

other words, there is no requirement that the claims be restricted to the working examples. Section 2164.03 of MPEP recites:

> the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (*In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir., 1991); *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971))

As further stated in section 2164.08 of MPEP:

> claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious (*In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970))... When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification.

See also *Application of Angstadt* (537 F.2d 498, 502-503, 190 USPQ 214, 218 [Cust. & Pat.App., 1976]) stating that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art." Similarly, in *In re Rasmussen*, court stated that "a claim may be broader than the specific embodiment disclosed in a specification" (650 F.2d 1212, 1215, 211 USPQ 323, 326 [Cust. & Pat.App., 1981]). Finally, in *In re Goffe* (542 F.2d 564, 567, 191 USPQ 429, 431 [CCPA 1976]), the court stated:

> To provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Applicants further respectfully submit that the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *See*, also, *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In light of the above-presented standards, amendments and arguments, it is believed that the present application provides an adequate enablement for the full range of receptor heterodimers encompassed by the present claims. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is believed to be overcome and withdrawal of such is kindly requested.

35 U.S.C. §102(b) and 35 U.S.C. §103 Rejections

In the Office Action, the Examiner has rejected claims 19 and 21-23 under 35 U.S.C. §102(b) as being anticipated by Knapp *et al.* (FASEB J., 1995, 9:516-25). The Examiner has also rejected claim 20 under 35 U.S.C. §103(a) as being obvious over Knapp *et al.* in view of Cvejic *et al.* (J. Biol. Chem., 1997, 272:26959-64) and further in view of Egan *et al.* (Science, 1981, 214:923-4). Both rejections are centered on the Examiner's interpretation that claims 19-23 recite a method for screening compounds which modulate an endogenous opioid heterodimer. The Examiner states that Knapp *et al.* teach that delta and kappa opioid receptors are found in rat brain and that various compounds have been screened which have binding affinity for these receptors.

The rejections are respectfully traversed. Applicants respectfully submit that none of the cited references disclose or suggest opioid receptor heterodimers as recited in the present claims. Claim 19 as amended recites that "both receptor subunits are heterologously expressed in a host cell" (emphasis added). None of the cited references disclose or suggest that opioid receptor heterodimers can be co-expressed in host cells which do not endogenously express the receptor subunits and used to screen for modulators.

In summary, none of the references cited by the Examiner anticipate or make obvious the present invention. Reconsideration and withdrawal of the anticipation and obviousness rejections is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 1-23 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: November 4, 2003

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1: Exp Cell Res. 2002 Nov 1;280(2):192-200. Related Articles, Link

ELSEVIER FULL-TEXT ARTICLE

Interactions of opioid and chemokine receptors: oligomerization of mu, kappa, and delta with CCR5 on immune cells.

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Activation of opioid receptors by morphine was previously shown to specifically induce the expression of chemokine receptor CCR5, promoting simian AIDS virus entry and replication in immune cells. The present study was undertaken to determine whether these two structurally and functionally distinct G-protein-coupled receptors are in close proximity and form an oligomeric complex in the cell membrane so that the activation of one triggers the activity of the other. Both human CEM x174 and monkey lymphocytes were used in this study and gave similar results. Immunoprecipitation experiments showed that CCR5, but not CD4 nor Na (+)/H(+) exchanger, coprecipitates with all three subtypes (mu, delta, and kappa) of opioid receptors. A single protein band immunoreactive with antibodies against both the CCR5 and the opioid receptors was identified after electrophoresis on nondenaturing polyacrylamide gels. Chemical crosslinking experiments using glutaraldehyde or BS(3) indicate that these receptors are closely situated on the cell membrane with an intermolecular distance less than 11.4A. Functional studies revealed that a combination treatment of cells with morphine, an agonist for mu, and MIP-1beta, a ligand for CCR5, suppresses the inhibitory effect of MIP-1beta and increases the stimulatory effect of morphine on CCR5 expression. These results suggest that oligomerization of chemokine receptor CCR5 and opioid receptors on th cell membrane of human or monkey lymphocytes may modulate receptor functions.

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